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# Ethylene Glycol

CAS #107-21-1

Swiss CD-1 mice, at 0.0, 0.5, 1.0, 1.5%, drinking water

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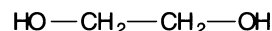
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Started 2/21/84; Completed 2/25/86

NTIS #PB86177383/AS

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Ethylene glycol (EG), an industrial chemical precursor, solvent, and component of antifreezes and numerous other consumer products, was tested for reproductive toxicity in Swiss CD-1 mice using the RACB protocol (Lamb et al., *Toxicol Appl Pharmacol* 81:100-112 [1985]). This study in particular was conducted as a follow-up to a previous EG study. This study used a higher top dose, and incorporated a crossover mating, and an evaluation of all dose levels in  $F_1$ s. Based on the data from the previous study, doses for this study were set at 0.0, 0.5, 1.0, and 1.5% EG in drinking water for approximately 21 weeks. Based on water consumption data collected during this study, these concentrations produced calculated EG consumptions of approximately 850, 1800, and 2800 mg/kg/day.

Body weight was not affected during the Task 2 cohabitation phase. While the number of litters per pair was unchanged, the number of pups per litter was reduced by approximately 15% at the top dose, and the pup weight adjusted for litter size was reduced by 3, 7, and 10% (low to high doses, respectively).

After the last litter was delivered and reared to weaning, the control and 1.5% EG  $F_0$  mice were cross-mated in Task 3 to determine the affected sex. While the number of pups per litter was the same as controls, the adjusted pup weight was 9%

lower than controls in the control male  $\times$  1.5% EG female group.

After the last Task 3 litter was delivered, the females were subject to vaginal lavage for 7 days, and then all control and 1.5% EG mice were necropsied. While female body weight was unchanged by 1.5% EG consumption, male body weights were reduced by 9%; organ weights were unaffected. Sperm motility at 1.5% EG was reduced by 15%, and the frequency of abnormal sperm rose from 5% (controls) to 8% (1.5% EG). Estrous cycle length was unaffected by EG exposure. No treatment-related microscopic lesions were seen in tissues of the 1.5% EG females. Renal tubule lesions were noted in 60% of male mice, concomitant with the presence of crystals presumed to be oxalate. Serum total calcium levels were the same across all dose groups.

All offspring from the last litter of  $F_1$ s were reared and dosed until mating at post-natal day  $74 \pm 10$ . Dosing continued through the week of mating and until sacrifice. There were no effects on the indices of mating and fertility, and the number of pups per litter was unchanged, but pup weight adjusted for litter size was reduced by 5, 5, and 6% in the low, middle, and high doses, respectively.

All dose groups of  $F_1$  mice were killed and necropsied after vaginal lavage. Female

body weight and weights of liver and kidney were not affected at any dose level, and male body weights were not different across dose groups. Absolute testis weight was reduced by 12, 15, and 15% as dose increased, and adjusted right epididymis weight was reduced by 9 and 11% in the middle and top dose groups, respectively.

Sperm count was reduced by 23, 18, and 17% as dose increased; only the first two were significant. The percent motile sperm was reduced by 3 and 12% in the middle and top dose groups, respectively. Estrous cycle length and characteristics were unchanged. Total serum calcium was measured in all dose groups and was not changed by EG exposure. Microscopically, there was a greater incidence and severity of testicular damage in the 1.5% EG males, but neither sex showed signs of renal damage or regeneration.

This study repeated the findings of facial structural abnormalities (cleft palate and ablepharon). These were seen in the middle and top dose groups and were also seen in Task 3 only in pups born to EG-exposed dams.

This repeat ethylene glycol study used a higher top dose to confirm the reproductive and developmental toxicities caused by ethylene glycol in Swiss mice. These were seen at and below doses that reduced  $F_0$  male body weights by 9%.

**Summary:** NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: PB86177383/AS

Chemical: Ethylene Glycol

CAS#: 107-21-1

Mode of exposure: Drinking water

Species/strain: Swiss CD-1 mice

F <sub>0</sub> generation	Dose concentration →	0.5%	1.0%	1.5%
General toxicity		Male, female	Male, female	Male, female
Body weight		—, —	—, —	—, —
Kidney weight <sup>a</sup>		•, •	•, •	—, —
Liver weight <sup>a</sup>		•, •	•, •	—, —
Mortality		•, •	•, •	•, •
Feed consumption		•, •	•, •	•, •
Water consumption		—, —	—, —	—, —
Clinical signs		•, •	•, •	•, •

Reproductive toxicity			
̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	—, ↓	—, ↓	↓, ↓
Cumulative days to litter	•	•	•
Absolute testis, epididymis weight <sup>a</sup>	•	•	—, —
Sex accessory gland weight <sup>a</sup> (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	—, ↓, ↑
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	1.5%	—

F <sub>1</sub> generation	Dose concentration →	0.5%	1.0%	1.5%
General toxicity		Male, female	Male, female	Male, female
Pup growth to weaning		•	•	•
Mortality		•	•	•
Adult body weight		—	—	—
Kidney weight <sup>a</sup>		—, —	—, —	—, —
Liver weight <sup>a</sup>		—, —	—, —	—, —
Feed consumption		•	•	•
Water consumption		•	•	•
Clinical signs		•	•	•

Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	↑, ↓	—, ↓	—, ↓
Absolute testis, epididymis weight <sup>a</sup>	↓, —	↓, ↓	↓, ↓
Sex accessory gland weight <sup>a</sup> (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	↓, —, —	↓, ↓, —	—, ↓, —
Estrous cycle length	—	—	—

Summary information	
Affected sex?	Both
Study confounders:	None
NOAEL reproductive toxicity:	Not reached, F <sub>0</sub>
NOAEL general toxicity:	?
F <sub>1</sub> more sensitive than F <sub>0</sub> ?	Unclear
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. <sup>a</sup>Adjusted for body weight.